Editorial Articles

Impact of laparoscopic surgery on immune function

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Summary

Objectives: Endoscopic surgery, mostly studied during laparoscopic hysterectomy or cholecystectomy, has no important effects on classic endocrine responses when compared with similar open operations but may slightly reduce inflammatory responses and various immune functions. Preservation of both systemic and intraperitoneal immunity is particularly important in surgery for intra-abdominal sepsis or cancer and thus an understanding of the impact of laparoscopy on immune function is relevant.

Methods: Substantial recent studies on the topic of immune response in general and gynecologic surgery were identified from Medline.

Results and discussion: The impact of laparoscopic surgery on the peri- and postoperative metabolic and systemic immune response is significantly less after laparoscopic hysterectomy or cholecystectomy than with an open approach.

Conclusion: Laparoscopic surgery better preserves the postoperative immunological functions. However, prospective randomized studies are necessary to see whether these potential advantages can be employed in common clinical practice.

Key words: Laparoscopy; Immune system; Stress response; Hysterectomy; Surgery.

Introduction

Surgical outcome has improved considerably in recent years because of advances in anesthesia, surgical technology, and perioperative care [1]. Over the past decade laparoscopic surgery has become integral to general surgical practice, with the advantages over an open operation of less postoperative pain, shorter hospital stay, reduced postoperative morbidity, earlier return to normal activity and better cosmetic outcomes demonstrated for a range of procedures. Furthemore, it seems likely that surgery is associated with significant suppression of immune function; the degree to which this occurs and its duration are determined by the magnitude of the initial surgical insult [2, 3]. Because laparoscopic surgery reduces surgical trauma, it may be associated with less systemic immune impairment [4, 5, 6]. While many studies have demonstrated a more favourable systemic immune response following laparoscopic surgery, the local immune system within the peritoneal cavity might act differently [2].

In the present review, an overview is given of the recent available literature, including our own data concerning laparoscopic hysterectomy and postoperative metabolic, inflammatory and immune changes.

Laparoscopic surgery and inflammatory response and immune function

The effect of laparoscopic techniques on immunological responses have been increasingly studied since the introduction of minimally invasive surgical techniques. In recent years, a number of trials have been performed concerning systemic immune response to laparoscopic surgery, both in animal models and in clinical settings [4, 7, 8, 9, 10]. The clinical findings show different results, which to some extent may be related to the small size of the randomized studies (Table 1).

Table 1. — *Effect of laparoscopic surgery on perioperative endocrine and immune functions.*

Author	Type of surgery	Parameter
Yuen (1998)	LPSC vs open hysterectomy	CRP*, IL-6*, WBC*, Cortisol*
Harkki-Sirén (2000)	LPSC vs open hysterectomy	CRP*, IL-6*, TATI~, Ca 125~
Holub (1999)	LPSC vs open hysterectomy	CRP*, CK *
Ellstrom (1996)	LPSC vs open hysterectomy	CRP~, IL-6~, Cortisol~
Joris (1992)	LPSC vs open cholecystectomy	CRP*, IL-6*, WBC*, Cortisol~
Redmond (1994)	LPSC vs open cholecystectomy	CRP~, WBC*, TNF*, Cortisol~

Abbrevations; *reduced response in laparoscopic vs open surgery ($p < 0.05$) . ~no difference between laparoscopic vs open surgery. LPSC = laparoscopy; CK = creatine kinase.

Cytokines and acute-phase response

Cytokines and acute-phase response (APR) are necessary for the immune function of the host, but overproduction or production at non-inflammatory sites may, in certain cases, leads to deleterious effects on the surrounding tissue [11, 12]. A reduced production of cytokines and, thereby, a reduction in the inflammatory response is therefore thought to be beneficial for the patient´s postoperative course [13]. C-reactive protein (CRP) is the most extensively studied APR protein; following surgery CRP levels usually rise approximately 4-12 hours after operation and peak at 24-72 hours. Postoperative CRP levels are significantly lower during the first three days after laparoscopy than after open surgery [4, 6, 7, 8]. On the other hand, in another clinical study of laparoscopic versus abdominal hysterectomy, Ellstrom *et al.* [9] found no differences in the levels of CRP between the different surgical approaches. Our findings differed from those of Ellstrom *et al.*, who reported no significant difference in the C-reactive protein [6]. However, patients who had a laparoscopic hysterectomy in Ellstrom's series had longer operating times, which might have obscured the benefit of less tissue trauma. Contrary to most of the reported trials comparing the laparoscopic and open approach to hysterectomy, our operating time for laparoscopic hysterectomy was short and similar to that for abdominal hysterectomy [6, 7, 14, 15, 16]. This eliminated the possible affect on anesthesia and analgesia on the stress response biochemical markers making the effects of tissue trauma readily demonstrable [7].

Surgical trauma is followed by release of cytokines from damaged tissue. The major cytokine is interleukin-6 (IL-6), which stimulates hepatic synthesis of APR proteins such as C-reactive protein and tumor-associated trypsin inhibitor (TATI). Tumor necrosis factor alfa (TNF-alfa) and interleukin-1(IL-1) are important cytokines in the activation of the systemic immune response and play a important role in initiating the cascade of inflammatory mediators and the subsequent activation of leukocytes that make up the immune response [13]. IL-1 stimulates the production of prostaglandins and nitric oxide, both of which are highly inflammatory. In addition, interleukin-1 induces the synthesis of chemokines, small proteins that facilitate the entry of neutrophils, macrophages, and lymphocytes into tissue [17].

Plasma IL-6 levels are known to be proportional to the magnitude of the surgical operation and a predictor of postoperative complications [18]. Malik *et al.* [19] reported a significant increase in the level IL-6 in patients undergoing abdominal hysterectomy at the time of peritoneal closure that reached a maximum two hours postoperatively when compared to the IL-6 levels of patients undergoing vaginal hysterectomy or laparoscopically assisted vaginal hysterectomy ($p < 0.05$). Harkki-Siren *et al.* [8] describe significant differences in postoperative IL-6 levels after laparoscopic hysterectomy, an observation which was has been confirmed by others [7]. However, the results concerning other surgical procedures show conflicting data. Hill *et al.* [20] reported that the response of inflammatory mediators to hernia repair is not modified by undertaking the procedure laparoscopically. Perhaps the magnitude of the surgical injury from an open hernia repair is not large enough to demonstrate any significant reduction in cytokine response after a minimally invasive surgical repair.

The available literature concerning inflammatory response and laparoscopic surgery is mostly obtained from reports of patients undergoing cholecystectomy or hysteretcomy and suggest reduced activation (IL-1, IL-6 and CRP) when compared with laparotomy. However, less frequently studied cytokines (IL-8), acute-phase proteins (TATI, fibrinogen, albumin and transferrin) and other surgical procedures show a less clear picture [13].

Non-specific immune response

Polymorphonuclear (PMN) leucocytes play a key role in the host defence against invading micro-organisms. Surgical stress affects PMN function during the postoperative period. Several studies have evaluated the total leucocyte count and specific leucocyte population following laparoscopic and open surgery, and have demonstrated a significant increase in overall peripheral leucocyte numbers following open, but not laparoscopic procedures [4, 10, 21]. Sietses *et al.* [22] did not observe any difference in systemic white blood cell counts between patients undergoing laparoscopic and those having open Nissen fundoplication. Holub *et al.* [23] compared electrosurgery versus harmonic scalpel in laparoscopic hysterectomy, and found in both a significant increase in white cell counts on the first day postoperatively. A significant difference in stimulated oxygen radical production has also been noted between the open and laparoscopic techniques, suggesting a higher state of PMN activation after the former [22]. IL-8 is one of the most important chemotactic cytokines for neutrophils. Decker *et al.* [24] reported significantly higher plasma levels after conventional surgery when compared with the laparoscopic approach .

During the last few years, it has become clear that monocytes and macrophages have strong inflammatory, phagocytic and tumoricidal functions and play a central role in immune function. The major histocompatibility-complex class-II surface antigen, human leukocyte antigen (HL-DR), expressed on the surface of monocytes and macrophages is critical in this interaction [25]. Sietses *et al.* [26] assessed postoperative immune function using HLA-DR expression in two different operative techniques of laparoscopic cholecystectomy.

The peripheral histamine response produced by mast cells exerts a variety of well recognized systemic effects (e.g. allergic, cardiovascular and inflammatory responses). Histamine also alters the function of granulocytes, macrophages and T lymphoctes [2]. Nies *et al.* [27] randomized 40 patients with acute cholecystitis to undergo either laparoscopic or open cholecystectomy and found significantly greater intraoperative and postoperative histamine levels in patients after the former procedure.

Significantly less activation, preserved serum factors and preserved polymorphonuclear function all correlate with clinical observation of fewer postoperative septic complications following laparoscopic surgery [2]. This suggests that a laparoscopic approach might be beneficial in the surgical management of acute pelvic inflammatory disease or peritonitis.

Delayed-type hypersensitivity (DTH) and T-cell function

DTH responses reflect alterations in T-lymphocyte populations in patients undergoing surgical procedures. However, DTH is a complex multifactorial phenomenon involving interactions among both lymphocytes and lymphocyte subpopulations which can affect the final response [2]. Although several studies have demonstrated that DTH is better preserved after laparoscopic surgery than after an open operation, it is still not clear which component of the whole cascade is responsible for the preservation of cellular immunological response [28].

Intraperitoneal immune function

The benefit of less systemic immune system suppresion following laparoscopic surgery may not necessarily be mirrored at the level of the peritoneal membrane. Apart from mechanical factors, the choice of insufflation gas and intraperitoneal pressure are also known to modulate the local immune enviroment. The peritoneal membrane plays a major role in the immunological response to abdominal surgery [2]. Badia *et al.* [29] observed sequentially raised cytokine levels in the peritoneal fluid following laparotomy and suggested that the systemic postoperative cytokine response may arise from the peritoneal cavity. Similarly, falls in perioperative and postoperative TNF-alfa levels have also been observed [30]. Immune function at the peritoneal level is very complex,and apart from tissue trauma, mechanical effects, intraperitoneal pressure and specific characteristics of the insufflation gas, other factors might also influence this function. Based on a limited number of reported studies it appears that the systemic immunological benefits observed after laparoscopic surgery may not apply at the peritoneal level [2].

Immune function, tumor growth and port-site metastasis (PSR)

Although it is likely that the aetiology of PSR is multifactorial, some experimental studies have suggested that local peritoneal immune depression may play an important role in the development of tumour metastases following laparoscopic surgery [31, 32]. Several investigators have demonstrated that the incidence of PSR can be reduced in experimental models by the exclusion of carbon dioxide from the laparoscopic enviroment using either gasless laparoscopy or insufflation with helium [33].

Immune suppresion may also be implicated in postoperative tumor metastasis formation. Especially important in this respect is the protection of the patient´s immunity during the first few days after surgery.

There are now various animal studies that have shown that cancer cells grow more aggressively and are established more easily after laparotomy than after peritoneal insufflation with carbon dioxide. Bouvy *et al.* [34] reported that laparoscopic surgery was associated with decreased tumor ex when compared with laparotomy. Allendorf *et al.* [35] found that tumor cells implanted intradermally in mice grew significantly faster after laparotomy than those in the control and carbon dioxide insufflation groups.

With regard to the issue of port-site metastases, current data suggest that the origin of these metastases is not related to immunological factors but rather to a facilitated implantation of malignant cells, either from contaminated instruments or indirectly due to mechanical effects of the insufflation gas [36].

Laparoscopic surgery and endocrine metabolic responses

It appears that most studies have compared laparoscopic and conventional open hysterectomy or cholecystectomy (Table 1). The results are relatively uniform in showing no significant differences in classic endocrine catabolic response (cortisol, catecholamines). Similarly, no important differences have been demonstrated in metabolic responses (glucose and protein economy), although a few studies have shown reduced responses in favor of laparoscopic surgery [1]. Ishizikuka *et al.* [37] compared adrenergic-sympatic responses during pelvic laparoscopic surgery with carbon dioxide insufflation with those during laparotomy. They concluded, that the arterial tension of carbon dioxide increases due to carbon dioxide insufflation are associated with adrenergic-symphathetic activation and hemodynamic changes during laparoscopic pelvic surgery. In conclusion, existing data do not suggest major or clinically relevant differences in endocrine metabolic responses between laparoscopic and open procedures.

Conclusion

It appears from data comparing laparoscopic and open surgery in a variety of operations that only small, if any, differences exist in various endocrine metabolic responses, inflammatory responses, and changes in immune functions, except for reduced CRP and IL-6 responses in hysterectomy and cholecystectomy. Furthemore, intraperitoneal immunity is complex, and this component of the immune system may behave independently of systemic immune function: the systemic benefits of laparoscopic surgery may not necessarily extend to the peritoneal interface. Nevertheless, it is still an attractive working hypothesis to consider the smaller tissue injury (wound size) with laparoscopic versus open surgery to have beneficial effects on outcome [2]. The important question remains as to why the advantageous outcome results are not more obvious.

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